REMARKS/ARGUMENTS

The amendments to the claims are fully supported by the specification and claims as originally filed and do not constitute new matter. Applicants believe that the current amendments place all claims in *prima facie* condition for allowance or, at least, in a better form for consideration on appeal. Accordingly, the consideration and entry of the present amendment after final rejection is respectfully requested.

Claims 58-63 have been amended to recite polypeptides comprising a polypeptide sequence having at least 80-99% amino acid sequence identity to the amino acid sequence of the polypeptide of SEQ ID NO:119, with or without its signal peptide sequence, or the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number209670. Support for polypeptides comprising polypeptide variants is found in the specification at, for example, page 108, line 38, to page 109, line 26.

Claim 66 has been canceled. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

Claims 58-65 and 68-70 are pending after entry of the instant amendment.

I. Priority

The Examiner states that the priority claim does not point out the proper lineage and relationships among the listed applications, and notes that not all members are co-pending and that multiple applications within the chain fail to support the content of SEQ ID NO:118 and SEQ ID NO:119. The Examiner states that Applicants are required to clarify the priority claim including all co-pending applications and their designated relationships upon which priority is claimed.

Applicants respectfully submit that the specification was previously amended in the manner requested by the Examiner in the Preliminary Amendment mailed August 21, 2002, a copy of which is enclosed. As this Preliminary Amendment does not appear to have been entered, Applicants have also amended the specification by amendment herein.

II. Specification

As requested by the Examiner, the priority claim has been amended to designate only

those applications which support the content of SEQ ID NO:118 and SEQ ID NO:119, identified as PRO320, and to clarify the priority lineage, including all co-pending applications and their designated relationships upon which priority is claimed.

III. Claim Objections

Claims 64, 65, and 68 are objected to as depending upon rejected base claims. Applicants respectfully submit that, with the amendments and arguments herein, all the claims are in condition for allowance, and the objections to the claims are moot.

IV. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 58-63, 66, and 69-70 remain rejected under 35 U.S.C. §112, first paragraph, as allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the claimed invention." In particular, the Examiner notes that "[t]he claims as written include polypeptides having at least 80-99% sequence identity with SEQ ID NO:119 and polypeptides including or lacking various regions including, lacking its signal peptide, the extracellular domain, the extracellular domain but lacking its signal peptide, but for which no particular biological activity or function is recited." Therefore, the Examiner asserts that "the instant disclosure of a single polypeptide, that of SEQ ID NO:119 with the instantly disclosed specific activities, does not adequately support the scope of the claimed genus." (Pages 6-7 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection.

Applicants respectfully submit that the cancellation of claim 66 renders the rejection of this claim moot.

The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the

specification for the claim language."[1] [2] The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis.[3] The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. [4] [5]

In *Environmental Designs, Ltd. v. Union Oil Co.*,[6] , the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." (Emphasis added).[7] Further, The "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art."[8] [9]

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[1] *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983).

[2] *See also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991).

[3] *See e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.

[4] *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

[5] *See also* M.P.E..P. §2163 II(A).

[6] 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

[7] *See also* M.P.E.P. §2141.03.

[8] *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added).

[9] See *also* M.P.E.P. §2141.03.

The Disclosure Provides Sufficient Written Description for the Claimed Invention

First, Applicants respectfully maintain the position that that Claims 58-65 and 68-70 satisfy the written description requirement under 35 U.S.C. §112, first paragraph, for the reasons previously set forth in the Applicants' response filed on December 30, 2004.

Secondly, Applicant respectfully submit that Claim 63 (and, as a consequence, those claims dependent from the same), directed to the polypeptide of SEQ ID NO:119, with or without its signal peptide sequence, meets the written description requirement under 35 U.S.C. §112, first paragraph. The Examiner acknowledges that Applicants have described the polypeptide sequence of SEQ ID NO:119. (Page 7 of the instant Office Action). As disclosed, for example, in Figure 45, the signal peptide sequence of SEQ ID NO:119 comprises amino acid residues 1-21.

Applicants respectfully submit that the instant specification evidences the actual reduction to practice of a full-length PRO320 polypeptide of SEQ ID NO:119, with or without its signal peptide sequence. As stated above, the Examiner has acknowledged that a polypeptide comprising the sequence set forth in SEQ ID NO:119 meets the written description provision of 35 U.S.C. §112, first paragraph. Thus, the genus of polypeptides with at least 80% sequence identity to SEQ ID NO:1, which possess the functional property of inhibiting endothelial cell growth would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description.

The specification describes methods for the determination of percent identity between two amino acid sequences. (See page 123, line 24 to page 125, line 14). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 180, line 9 to page 183, line 8) This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 182). The specification describes methods for one of ordinary skill in the art to identify polypeptides having at least 80% identity to SEQ ID NO:119 wherein the polypeptide inhibits endothelial cell growth. Specifically, Example 109 sets forth an assay for determining whether a native polypeptide having at least 80% identity to

PRO320 inhibits VEGF stimulated proliferation of endothelial cells. Thus one of ordinary skill in the art would have understood at the time of filing what was encompassed by the claims.

The Examiner acknowledges the addition of the functional recitation. The Examiner asserts, however, that "the arguments fail to present objective evidence of any additional species of any percent identity or portion thereof as encompassed by the extracellular domain recitation that exhibits the noted function." (Page 12 of the instant Office Action).

Without acquiescing to the Examiner's position, and solely in the interest of expediting prosecution in this case, as amended, the term "extracellular domain" is no longer present in Claims 58-63 (and, as a consequence, those claims dependent from the same). Claim 66 has been canceled.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the written description rejections under 35 U.S.C. §112, first paragraph.

IV. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 58-70 are rejected under 35 U.S.C. §112, first paragraph, allegedly "because the specification, while being enabling for SEQ ID NO:119 exemplified as exhibiting activity [as shown in] Example 109..., does not reasonably provide enablement for the variable peptide sequences and for such generic sequences where no requisite functional activity is provided as claimed." The Examiner further asserts that "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims." (Pages 9-10 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection.

Applicants submit that the cancellation of Claim 66 renders the rejection of this claim moot.

The Legal Test for Enablement

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure provided by applicants coupled with information known in the art at the time the invention was made, without undue experimentation. [10] [11] Accordingly, the test

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[10] M.P.E.P. §2164.01.

[11] *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998)).

for enablement is not whether any experimentation is necessary, but whether, if experimentation is required, it is undue.[12] The mere fact that an extended period of experimentation is necessary does not make such experimentation undue.[13] [14]

A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re* Wands factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2) the level of one of ordinary skill in the art; 3) guidance provided in the specification, 4) the state of the prior art, and 8) the breadth of the claims.

"How a teaching is set forth, by specific example or broad terminology, is not important."[15] [16] "Limitations and examples in the specification do not generally limit what is covered by the claims" M.P.E.P. § 2164.08. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.[17]

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[12] *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (C.C.P.A. 1976).

[13] *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (C.C.P.A. 1977).

[14] M.P.E.P. §2164.06.

[15] M.P.E.P. §2164.08.

[16] *In re Marzocchi*, 439 F. 2d 220, 223-4, 169 USPQ 367, 370 (C.C.P.A. 1971).

[17] *Enzo Biochem., Inc. v. Calgene, Inc.,* 188 F.3d 1362, 1372 (Fed. Cir. 1999) (quoting *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991)).

The specification provides sufficient information to enable the claimed invention

Applicants have clearly provided the full-length sequence of SEQ ID NO:119 for the PRO320 polypeptide, thus one skilled in the art would easily know how to make the polypeptide, with or without the identified signal peptide sequence. In addition, PRO320 was demonstrated to inhibit VEGF stimulated proliferation of endothelial cells. Therefore, based on this information one skilled in the art would have known at the time of filing how to use the PRO320 polypeptide (SEQ ID NO:119) for inhibiting endothelial cell growth in mammals where such an effect would be beneficial, e.g., for inhibiting tumor growth. Accordingly, Claim 63 (and, as a consequence, those claims dependent from the same) meets the enablement requirement under 35 U.S.C. §112, first paragraph.

Applicants have provided native PRO320 sequence SEQ ID NO:119. The present application also describes methods for identifying polypeptides which inhibit VEGF stimulated proliferation of endothelial cells. Example 109 of the present application provides a detailed protocol for the VEGF stimulated proliferation of endothelial cell growth assay. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO320 protein is an inhibitor of endothelial cell growth. The specification further describes methods for the determination of percent identity between two amino acid sequences. (See page 123, line 24 to page 125, line 14). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. Accordingly, one of skill in the art could identify whether the variant PRO320 native sequence falls within the parameters of the claimed invention. Once such an amino acid sequence was identified, the specification sets forth methods for making the amino acid sequences (see page 180, line 9 to page 184, line 35) and methods of preparing the PRO polypeptides (see page 184, line 37 and onward).

Therefore, Applicants respectfully submit that one of skill in the art could readily test a variant polypeptide to determine whether it inhibits endothelial cell growth by the methods set forth in Example 109. Furthermore, one of ordinary skill in the art has a sufficiently high level of technical competence to identify sequences with at least 80% identity to SEQ ID NO:320. Accordingly, one of ordinary skill would know how to make and use the claimed invention without undue experimentation.

The Examiner acknowledges the addition of the functional recitation. The Examiner

asserts, however, that "the arguments fail to present objective evidence of any additional species of any percent identity or portion thereof as encompassed by the extracellular domain recitation that exhibits the noted function." (Page 12 of the instant Office Action).

Without acquiescing to the Examiner's position, and solely in the interest of expediting prosecution in this case, as amended, the term "extracellular domain" is no longer present in Claims 58-63 (and, as a consequence, those claims dependent from the same). Claim 66 has been canceled.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the enablement rejections under 35 U.S.C. §112, first paragraph.

V. Claim Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 58-63, 66, and 69-70 remain rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Without acquiescing to the Examiner's position, and solely in the interest of expediting prosecution in this case, as amended, the term "extracellular domain" is no longer present in Claims 58-63 (and, as a consequence, those claims dependent from the same). Claim 66 has been canceled. Hence, the rejection is believed to be moot, and should be withdrawn.

VI. Claim Rejections Under 35 U.S.C. §102

Claims 58-63, 66, and 69-70 remain rejected under 35 U.S.C. §102(e) as being anticipated by Ford *et al.,* U.S. Patent No. 6,392,018, filed February 12, 1999 and issued May 21, 2002.

Applicants respectfully submit that the Declaration of Dr. Ferrara, Dr. Goddard, Dr. Godowski, Dr. Gurney and Dr. Wood, as discussed in the Response filed November 29, 2004, and submitted with the Supplemental Response filed February 10, 2005, shows that the invention claimed in the present application was conceived and reduced to practice prior to February 12, 1999.

The Examiner asserts that "Applicants' arguments have been fully considered but are not persuasive to the noted claims with respect to homology and 'extracellular domains' which structural scope has not been clarified." The Examiner further asserts that "[p]ending

clarification to the metes and bounds of the 'extracellular domains' of the instant claims in context with percent variability, the Examiner cannot conclude that the prior art claims are not drawn in part to the same invention claimed." (Pages 15-16 of the instant Office Action).

Without acquiescing to the Examiner's position, and solely in the interest of expediting prosecution in this case, as amended, the term "extracellular domain" is no longer present in Claims 58-63 (and, as a consequence, those claims dependent from the same). Claim 66 has been canceled. Hence, the rejection is believed to be moot, and should be withdrawn.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2630 P1C5**).

Respectfully submitted,

Date: July 12, 2005

By: _____
Barrie Greene (Reg. No.46,740)

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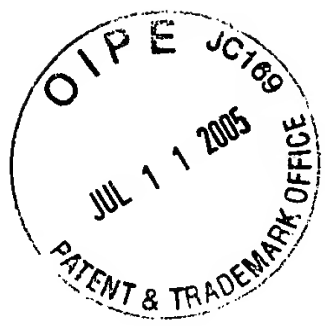

In Re Application of: Avi Ashkenazi et al
Serial No: 09/978,187
Filed on: October 15, 2001
Mailed on: August 21, 2002

Docket No: P2630P1C5
By: Elizabeth M. Barnes
Reg. No.: 35,059

The following has been received by the U.S. Patent Office on the date stamped.

_x_ Preliminary Amendment
_x_ Post card

Patent Docket P2630P1C5

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Avi Ashkenazi et al Serial No.: 09/978187 Filed: 10/15/2001	Group Art Unit: Not yet assigned Examiner: Not yet assigned CERTIFICATE OF MAILING I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on August 21, 2002 Yvonne Carter

PRELIMINARY AMENDMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Prior to substantive examination of the above captioned patent application, Applicants respectfully request that the following amendments be entered.

In the specification:

Please delete the paragraph at page 1, line 2, that was previously added by preliminary amendment.

Please insert the following new paragraph at page 1, line 2:

--RELATED APPLICATIONS

This application is a continuation of, and claims priority under 35 USC §120 to, US Application 09/918585 filed 7/30/2001, which is a continuation of, and claims priority under 35 USC §120 to, PCT Application PCT/US00/04341 filed 2/18/2000, which is a continuation-in-part of, and claims priority

under 35 USC §120 to, PCT Application PCT/US99/28565 filed 12/2/1999, which is a continuation-in-part of, and claims priority under 35 USC §120 to, US Application 09/380138 filed 8/25/1999, now abandoned, where US Application 09/380138 is the National Stage filed under 35 USC §371 of PCT Application PCT/US99/05028 filed 3/8/1999, which claims priority under 35 USC §119 to US Provisional Application 60/078004 filed 3/13/1998.--

REMARKS

The original paragraph at page 1, line 2 has been deleted. A new paragraph beginning at page 1, line 2 has been added in the specification. The new paragraph lists the documents to which priority is claimed for the instant application. Applicants respectfully request entry of this paragraph for prosecution in this application. The Examiner is invited to contact the undersigned at (650) 225-4563 if any issues may be resolved in that manner.

Respectfully submitted,

GENENTECH, INC.

Date: August 21, 2002

By: Elizabeth M. Barnes

Elizabeth M. Barnes, Ph. D.
Reg. No. 35,059
Telephone: (650) 225-4563

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

The paragraph at page 1, line 2 that had been added by a previous preliminary amendment has been deleted. A new paragraph beginning at page 1, line 2 has been added to replace the deleted paragraph.